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Commissioner of Patents and Trademarks

4422

File

Office Action Summary	Application No. 09/388,221	Applicant(s) Reed
	Examiner Anne Marie S. Beckerleg	Group Art Unit 1632

☒ Responsive to communication(s) filed on *Nov 17, 2000*.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1, 2, 4-28, and 30-66* is/are pending in the application.

Of the above, claim(s) *10, 12-17, 19-26, 28, 30-37, and 39-65* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1, 2, 4-9, 11, 18, 27, 38, and 66* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Applicant's amendment and arguments received on 11/17/00 has been entered. Claims 3 and 29 have been canceled. New claim 66 has been entered. Claims 10, 12-17, 19-26, 28, 30-37, 39-65 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention. Applicant timely traversed the restriction (election) requirement in Paper No. 9. The restriction requirement was not made final in the previous office action, paper no. 12, as the grouping of claim 28 was changed. The applicant has not made presented any arguments concerning the change in the restriction requirement for claim 28. Therefore, the restriction requirement is made **final**. Claims 1-2, 4-9, 11, 18, 27, 38, and 66 are pending and active in the instant application. An action on the merits follows.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The rejection of claims 1-2, 4-9, 11, 18, and 27 under 35 U.S.C. 112, first paragraph, for lack of written description has been modified to include claim 38 and new claim 66. Applicant's arguments as applicable to the instant rejection have been fully considered but have not been found persuasive in overcoming the instant grounds of rejection for reasons or record as discussed in detail below.

The specification discloses isolated DNA encoding a biologically active NAC which hybridizes with high stringency to DNA consisting of SEQ ID Nos: 1, 3, or 5, or DNA encoding the amino acid sequences set forth in SEQ ID Nos: 2, 4, or 6, and functional fragments of those sequences. The specification fails to provides sufficient guidance as to the nucleic acid or amino acid sequence characteristics for a "NAC" of the instant invention which are responsible for any type of biological activity. Further, it is well known in the art that even under high stringency conditions, numerous nucleic acid sequences will be capable of binding which are not 100% identical to the wild type sequence. The specification fails to describe the effects of any nucleic acid or amino acid changes on any biological activity of the proteins encoded by SEQ ID Nos: 1, 3, or 5, or set forth in SEQ ID Nos: 2, 4, or 6. *Vas-Cath Inc. v. Mahurkar,* 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is claimed." (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116). In the absence of any description of the biological

activity of the encoded "NAC" proteins, the skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides which may share those characteristics, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention. See *Fiers v. Revel,* 25 USPQ2d 1602 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Ltd.,* 18 USPQ2d 1016. Therefore, in view of the lack of description of isolated nucleic acids encoding a biologically active NAC as detailed above, the specification does not meet the written description provision of 35 U.S.C. 112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision.

In regards to applicant's argument that the specification provides a specific written description of the "functional fragments" claimed in new claim 66, it is noted that the demonstration that the NB-ARC or CARD domains of the instant "NAC"sequences are capable of homodimerization or binding with previously identified NB-ARC or CARD domains in other proteins does not correlate the binding ability of the instant domains with any affect on any biological process in any cell.

The rejection of claims 1-2, 4-9, 11, 18, 27, and 38 under 35 U.S.C. 112, first paragraph, for lack of enablement is withdrawn in view of following new grounds of rejection of the claims.

Claims 1-2, 4-9, 11, 18, 27, 38, and 66 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated nucleic acid encoding an NB-ARC and CARD containing protein (NAC) selected from DNA consisting of SEQ ID Nos: 1, 3, or 5, or DNA encoding the amino acid sequences set forth in SEQ ID Nos: 2, 4, or 6, and oligonucleotides capable of hybridizing with SEQ ID Nos: 1, 3, or 5, does not reasonably provide enablement functional fragments of the above, DNA encoding a biologically active NAC which hybridizes to the DNA molecules identified above with high stringency, or which is degenerate to those nucleic acids, or for methods of modulating the level of apoptosis in a cell by introducing the above identified sequences into the cell. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to the invention commensurate in scope with these claims.

The specification does not provide sufficient guidance concerning the biological activity of the "NAC" proteins of the instant invention. The specification teaches three novel mRNA splice variants whose protein coding region has regions homologous to an NB-ARC domain and a CARD domain. The specification also teaches that these domains are capable of homodimerization and are further capable of interacting *in vitro* with the NB-ARC or CARD domains respectively of other "NAC" proteins such as CED-4. It is noted that the specification defines a "NAC" protein as a protein which comprises an NB-ARC domain and a CARD domain. According to this definition, many NAC proteins were reported in the art at the time of filing. These proteins differ in their biological properties and functional activity. Some inhibit apoptosis,

some induce apoptosis, and some have no effect on apoptosis but rather affect cytokine expression and inflammatory reactions. Aside from demonstrating *in vitro* protein:protein interactions between the novel NB-ARC and CARD domains of the instant invention and several taught by the art, the specification does not provide any guidance as to any specific biological activity of the novel "NAC" proteins encoded by the disclosed cDNA or demonstrate that any of the disclosed proteins or protein domains or fragments have any apoptosis modulating activity either *in vitro* or *in vivo*. Several publications document the unpredictability of attributing function based on sequence similarity. See in particular Gerhold et al. (1996) BioEssays, Vol. 18, No. 12, 973-981, Wells et al. (1997) J. Leuk. Biol., Vol. 61 (5), 545-550, and Russell et al. (1994) J. Mol. Biol., Vol. 244, 322-350. Thus, the sequence similarity between the disclosed "NAC" sequences and proteins with known biological activities such as CED-4 does not overcome the unpredictability of determining the biological activity of a particular protein sequence in the absence of factual evidence.

Further, while the specification has identified putative "NB-ARC" like and "CARD" like domains, the specification provides no guidance as to how changes in the amino acid sequence of these regions or in any flanking regions or other identified putative domains affects any specific biological activity of the instant disclosed NAC proteins. It was well known at the time of filing that for nucleic acids as well as for proteins even a single nucleotide or amino acid change or mutation can destroy or substantially change the function of the biomolecule. The effects of these changes are largely unpredictable as to which ones will have a significant effect on structure,

folding, activity etc. For example, Ding et al. teaches that a single conservative amino acid substitution of alanine with isoleucine in IL-10 converts the protein to an immunostimulatory rather than an immunoinhibitory molecule and that "this single conservative residue alteration significantly affects ligand affinity for receptor". In terms of nucleic acid sequences which bind with "high stringency" to the SEQ ID Nos. 1, 3, and 5, it is noted that the act of hybridization between two DNA molecules results in non-specific binding depending on the length of the DNA and the hybridization conditions. While the "high stringency" conditions recited by the specification reduce the amount of non-specific binding, it is clear that the conditions allow for the binding of numerous sequences with less than 100% sequence identity. In the absence of any teachings as to the specific biological activities of the proteins encoded by SEQ ID Nos: 1, 3, or 5, it would have required undue experimentation to determine which of the numerous possible sequences which might bind to those sequences under "high stringency" would have the same biological activity as the wild type sequences. Thus, in the absence of any specific teachings in the specification concerning the actual biological properties of the predicted polypeptides encoded by SEQ ID Nos. 1, 3, or 5, or set forth in SEQ ID NOS: 2, 4, or 6, the art recognized unpredictability of attributing particular function properties to a polypeptide based on sequence similarity, the art recognized differences in function between proteins containing NB-ARC and CARD domains, and the breadth of the claims, it would have required undue experimentation to practice the scope of the invention as claimed.

The specification does not provide an enabling disclosure for modulating apoptosis by introducing the disclosed "NAC" encoding nucleic acids to a cell *in vitro* or *in vivo*. As discussed above, the specification does not demonstrate any specific biological activity for the disclosed proteins encoded by SEQ ID Nos: 1, 3, or 5. As also noted above, the art teaches that proteins containing NB-ARC and CARD domains range in activity from inducing apoptosis to inhibiting apoptosis to having no affect on apoptosis at all. In the absence of any factual evidence, it is unclear what if any effect the disclosed proteins would have in any particular cell on any apoptotic pathway. The disclosure that the NB-ARC or CARD domains of the instant "NAC" are capable of homodimerization or binding with previously identified NB-ARC or CARD domains in other proteins does not correlate the binding ability of the instant domains with any affect on any biological process in any cell. Further, the specification reads on modulating apoptosis in cells *in vivo*. The specification does not provide sufficient guidance for introducing and expressing a "NAC" protein in cells *in vivo* such that the level of "NAC" expression results in any effect on apoptosis in the animal. The art at the time of filing recognized the unpredictability of therapeutic levels of gene expression *in vivo*. Verma et al. teaches that," ... the lack of efficient delivery systems, lack of sustained expression, and host immune reactions - remain formidable challenges" in gene therapy, and specifically identifies the "Achilles heel" of gene therapy as gene delivery (Verma et al. (1997) Nature, Vol. 389, page 239, column 1, paragraph 1, and column 3, paragraph 2). Among the many problems associated with gene expression *in vivo*, Verma et al. teaches that the choice of an appropriate enhancer-promoter combination is critical to the level

and consistency of gene expression from a particular vector and that , " .. the search for such combinations is a case of trial and error for a given type of cell" (Verma et al. (1997) Nature, Vol. 389, page 240, column 2, paragraph 2, and column 3, line 1). Marshall et al. concurs, stating that, " difficulties in getting genes transferred efficiently to target cells- and getting them expressed- remain a nagging problem for the entire field", and that, "many problems must be solved before gene therapy will be useful for more than the rare application" (Marshall et al. (1995) Science, Vol. 269, page 1054, column 3, paragraph 2, and page 1055, column 1). Orkin et al. further states, " .. none of the available vector systems is entirely satisfactory, and many of the perceived advantages of vector systems have not been experimentally validated", that, "[m]ajor difficulties at the basic level include shortcomings in all current gene transfer vectors and an inadequate understanding of the biological interaction of these vectors with the host", and that "[w]hile the expectations and the promise of gene therapy are great, clinical efficacy has not been definitively demonstrated at this time in any gene therapy protocol.." (Orkin et al. (1995) Report to the NIH, page 1, paragraphs 3-4, and page 8, paragraph 2,). Thus, due to the art recognized unpredictability of achieving therapeutic levels of gene expression using vectors available at the time of filing, the lack of guidance provide by the specification concerning the biological activities of proteins encoded by SEQ ID Nos: 1, 3, or 5, the lack of correlation between the specification's working examples and any demonstration of any effect on apoptosis, the lack of guidance provided by the specification for the parameters affecting "NAC" gene delivery and expression *in*

vivo as discussed above, and the breadth of the claims, it would have required undue experimentation to practice the invention as claimed.

In response to the previous rejection under 35 U.S.C. 112, first paragraph, the applicant's argue that new claim 66 recites functional fragments that are disclosed in the specification and that the specification as a whole provides extensive guidance for achieving *in vivo* gene transfer such that one of skill in the art would reasonably expect NAC expression to modulate apoptosis as claimed. As discussed above, the disclosure that the NB-ARC or CARD domains of the instant "NAC"sequences are capable of homodimerization or binding with previously identified NB-ARC or CARD domains in other proteins does not correlate the binding ability of the instant domains with any affect on any biological process in any cell. Further, as also discussed in detail above, the specification's general guidelines concerning gene delivery *in vivo* does not overcome the high degree of unpredictability for therapeutic gene expression *in vivo* taught in the art. It is noted that the unpredictability of a particular art area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991). It is also well established in case law that the specification must teach those of skill in the art how to make and how to use the invention as broadly claimed. In re Goodman, 29 USPQ2d at 2013 (Fed. Cir. 1994), citing In re Vaeck, 20 USPQ2d at 1445 (Fed. Cir. 1991). 35 U.S.C. § 112 also requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art. In re Fisher, 166 USPQ 18, 24 (CCPA 1970). Therefore, applicant's arguments, having

been fully considered, have not been found persuasive in overcoming the instant grounds of rejection of the claims for reasons or record as discussed in detail above.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

New claim 66 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 66 recites the limitation "the nucleic acid aid according to claim 1". There is insufficient antecedent basis for this limitation in the claim. This rejection can be overcome by deleting the word "aid" from claim 66.

Claim Rejections - 35 USC § 102

The rejection of claim 38 under 35 U.S.C. 102(b) over Seshagiri et al. is withdrawn in view of applicant's amendment to the claim.

The rejection of claims 2, 8, 9, 11, 27, and 29 under 35 U.S.C. 102(a) over Nagase et al. is withdrawn in view of new grounds of rejection of the claims under 102/103.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 8, 9, 11 and 27 are newly rejected under 35 U.S.C. 102(a) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Nagase et al. (1999) DNA Res. Vol. 6, 63-70. The applicant claims oligonucleotides comprising at least 15 -1035 nucleotides capable of specifically hybridizing with a nucleotide sequence set forth in any of SEQ ID Nos: 1, 3, and 5, said oligonucleotides s which are labeled with a detectable marker, kits containing said oligonucleotides, and methods of detecting NAC nucleic acids using said oligonucleotides.

Nagase et al. teaches novel cDNA clones from human brain cDNA libraries which have large regions (>2800 bp) of 100% sequence identity to SEQ ID Nos: 1, 3, and 5 (see page 66, Table 2) and which are part of the HUGE human sequence database. Nagase et al. further teaches

the use of RT-PCR ELISA for identifying the expression pattern of the novel cDNAs in various cell types. While Nagase et al. does not disclose in this publication the characteristics of the oligos used in the RT-PCR ELISA assay, Nagase et al. teaches that the details of the methodology used can be found in a previous publication by the authors, Nagase et al. (1998) DNA Res. Vol. 5, 277-286. This referenced publication teaches that the oligonucleotides are labeled with digoxigenin (DIG)-11-dUTP and that the exact sequences of the primers used can be obtained from the authors. In fact, the sequences of all the primers used by the authors in generating the HUGE database are available on the internet at www.kazusa.or.jp. These oligomers are 21mers. Thus, Nagase et al., by teaching (DIG)-11-dUTP labeled 21 base pair oligomers with 100% sequence identity to SEQ ID Nos: 1, 3, and 5 and the use of said oligos to detect mRNA expression in cells, anticipates the invention as claimed.

Alternatively, based on the 21mer primer pairs disclosed on www.kazusa.or.jp website and the referenced teachings of Nagase et al. (Nagase et al. (1998) DNA Res. Vol. 5, 277-286) that oligos labeled with (DIG)-11-dUTP are used in RT-PCR ELISA, it would have been *prima facie* obvious at the time of filing to use 21mer oligos labeled with (DIG)-11-dUTP to identify sequences SEQ ID Nos: 1, 3, and 5 using RT-PCR ELISA. Further, based on the successful results obtained by Nagase et al. in detecting mRNA expression using RT-PCR ELISA, the skilled artisan would have had a reasonable expectation of success in making and using said oligos to detect NAC nucleic acids.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne Marie S. Beckerleg, Ph.D., whose telephone number is (703) 306-9156. The examiner can be reached Mon-Thurs and every other Friday from 8:30-6:00. General inquiries should be directed to the group receptionist whose phone number is (703) 308-0196. The official fax number is (703) 308-4242.

Dr. A.M.S. Beckerleg